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Cytolytic vaginosis: A brief review

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ABSTRACT

Cytolytic vaginosis is a condition that symptomatically mimics vulvovaginal candidiasis. It was reported for the first time by Cibley and Cibley, in 1991. The authors stressed the need to distinguish cytolytic vaginosis from vulvovaginal candidiasis since the symptoms were attributed to hyperacidity created by the overgrowth of resident lactobacilli of the vagina. Patients show lack of response to antifungals and therapy aimed at increasing the vaginal pH offers relief. Since then there were conflicting opinions regarding the existence of the entity "cytolytic vaginosis." This review aims to give a brief overview of the condition termed "cytolytic vaginosis."

Keywords: Cytolytic vaginosis, Vulvovaginal candidiasis, Overgrowth, Lactobacilli, Vagina

INTRODUCTION

Dysbiosis means imbalance of bacterial communities.[1] In other words, it refers to any change in the composition of resident commensal communities at a particular body site relative to the same found in healthy individuals.[2] However, the terminology "dysbiosis" becomes complicated with respect to the vaginal microbiome since the latter shows fluctuations in a woman's life span and also during a menstrual cycle.[1] The standard concept of vaginal dysbiosis points to a depletion of resident lactobacilli. This concept is challenged with the introduction of the entity cytolytic vaginosis, wherein an overgrowth of lactobacilli and variations in the frequencies of different species of lactobacilli constituting the vaginal microbiota lead to symptoms mimicking vulvovaginal candidiasis.[1]

Cibley and Cibley in their paper published in 1991, highlighted an entity "cytolytic vaginosis" and laid down the diagnostic criteria.[3] The authors suggested that many of the cases perceived as treatment-resistant vulvovaginal candidiasis could actually be cytolytic vaginosis. The authors considered cytolytic vaginosis, a better terminology than Doderlein's cytolysis as only a few species of lactobacilli are Doderlein's bacilli.[3] The name is derived from the characteristic feature "vaginal epithelial cell lysis" that is associated with the condition, which in turn, is produced by the abundant growth of lactobacilli.[3]

EPIDEMIOLOGY

The frequency of cytolytic vaginosis varied from 1.7% to 16.3% [Table 1] in previous studies.[4-9] A study conducted among patients attending the gynecology department showed a frequency of 16.3% and the author opined that cytolytic vaginosis is not an uncommon disease and attributed the reported low frequency to misdiagnosis of the condition as vulvovaginal candidiasis.[7] Yang

Table 1: Studies on cytolytic vaginosis.

Study	Study participants	Number of study participants	Frequency of cytolytic vaginosis
Cerikcioglu and Beksac	Women with symptoms suggestive of vulvovaginal candidiasis	210	7.1%
Demirezen	Patients with symptoms resembling those of candidal vaginitis	2947	1.8%
Hacisalihoglu and Acet	Retrospective evaluation of cervical smear specimens from two centers from 2015 to 2018	3000 specimens	1.7%
Puri	Patients attending the gynecology outpatient department during one year and whose cervical smears showed evidence of inflammation	190	16.3%
Yang *et al.*	Women with single infection-recurrent vulvovaginitis (four acute episodes of vaginal infection within a year)	484	26.7%
Wathne *et al.*	Fertile women (15–50 years of age) seeking consultation due to vaginal discharge and/or genital malodor	101	5%

et al., in a study of 484 women with single infection-recurrent vulvovaginitis (defined as at least four acute episodes of vaginal infections in a year) found cytolytic vaginosis (26.7%) to be the second most common disease after vulvovaginal candidiasis (36.6%).[8]

The common age group affected is 18–40 years.[4,6,8] Symptoms of cytolytic vaginosis are more severe during the luteal phase of the menstrual cycle.[10] It is reported that women with diabetes mellitus could be at a higher risk for cytolytic vaginosis. A high serum glucose level is considered to favor the overgrowth of lactobacilli.[11]

PATHOGENESIS

Understanding the pathogenesis of cytolytic vaginosis requires a basic understanding of the normal vaginal microbiota.

The vagina has a non-keratinized, stratified squamous epithelium overlaid by a mucosal layer. This is continually lubricated by the cervicovaginal fluid. All these together, provide a physical and biochemical barrier against the invading organisms. The vagina harbors many microorganisms that constitute the vaginal microbiota.[10]

The vaginal microbiota change with the hormonal fluctuations that take place during the reproductive life of women (menarche, pregnancy, and menopause). In the pre-pubertal age group, vaginal microbiome is dominated by anaerobes such as *Escherichia coli*, diptheroids, and coagulase-negative *Staphylococcus* and shows less amounts of glycogen. The rise in estrogen at puberty promotes maturation and proliferation of vaginal epithelial cells and favors the accumulation of glycogen within them. Human α-amylase catabolizes glycogen to maltose, maltotriose, and α-dextrines, which in turn are metabolized by *Lactobacillus* species to lactic acid. The acidic environment created (pH 3.5–4.5) facilitates the growth of *Lactobacillus* species and contains the growth of the anaerobes. This dominance of *Lactobacillus* species declines with the decrease in estrogen levels that follows menopause. The vaginal microbiota are predominated by lactobacilli in normal pregnancy. This is attributed to the increased vaginal glycogen deposition that occurs during pregnancy under the influence of high estrogen levels. Menstruation is associated with a 100-fold decrease in *Lactobacillus crispatus* and increase in *Lactobacillus iners* and anaerobes such as *Gardenerella vaginalis (G. vaginalis)* and *Prevotella bivia*. In summary, estrogen, glycogen, and lactobacilli are instrumental in creating the normal acidic vaginal pH in women of the reproductive-age group.[10]

The importance of lactobacilli in maintaining a healthy vaginal milieu was known since the discovery of a vaginal bacillus by Albert S Döderlein, which he named as *Döderlein's bacillus* in 1892.[12,13] This was later renamed as *Lactobacillus*. Lactobacilli, derived mainly from the intestinal microbiota, play an important role in the defence against the invasion of opportunistic pathogens.[10,12] The major role of lactobacilli is to maintain the vaginal pH between 3.8 and 4.4. This acidic pH inhibits the growth of most of the pathogenic bacteria.[12]

The predominant *Lactobacillus* spp. that constitute the physiological vaginal microbiota in reproductive-age women are *L. crispatus*, *Lactobacillus gasseri*, *L. iners*, and *Lactobacillus jensenii*.[10] Lactobacilli are deficient in heme. The bacilli use O_2 to form H_2O with the help of flavoproteins. The enzymatic action of flavoproteins, when combined with the lack of the heme protein catalase, results in abundant production of H_2O_2. This in turn kills or inhibits other bacteria. Enzyme peroxidase (found in milk, saliva, cervical mucus, and other genital tract secretions, neutrophils, monocytes, and eosinophils) in the presence of a halide ion, enhances the bactericidal property of H_2O_2.[3] Thus lactobacilli keep the anaerobes such as *Gardenerella, Mobiluncus*, *Prevotella*, and *Ureaplasma* (causative organisms for bacterial vaginosis) in check.[10] It is reported that lactobacilli show antifungal property and protect against vaginal candidiasis through other mechanisms as well.[14] They produce small molecules called bacteriocins and biosurfactants. Bacteriocins have antifungal property while biosurfactants inhibit the attachment of *Candida* to the vaginal epithelial cell wall.[14]

The normal vaginal flora is considered as 5 lactobacilli per 10 squamous cells.[7] At times, for reasons yet to be clearly delineated, an overgrowth of lactobacilli occurs in the vaginal microbiota.[7] This in turn produces hyper acidity and low pH (≤3.8). This over-acidification results in damage to vaginal epithelium and causes lysis of epithelial cells which can be demonstrated as numerous bare nuclei and debris cytoplasm in a wet smear.[3] A causative role is suggested for the hormone progesterone, since the condition is more commonly observed during the luteal phase of menstrual cycle, pregnancy, and perimenopause. Despite the abundance of lactobacilli, the condition produces symptoms mimicking vulvovaginal candidiasis (itching, burning, irritation, dyspareunia, dysuria, and white cheesy vaginal discharge) and is referred to as cytolytic vaginosis. The symptoms are attributed to the low pH and the resultant over-acidification.[1]

Beghini *et al*., in a study on women with vaginal disorders noted elevated L-Lactic acid levels in the vaginal secretions from women with cytolytic vaginosis.[15] Xu *et al*., in a study using high-throughput sequencing, found an abundance of *L. crispatus* in patients with cytolytic vaginosis, while healthy women showed an abundance of *Lactobacillus* species L-YJ in the vaginal microbiome.[16]

However, in a review published in 2020, Voytik and Nyirjesy opined that "cytolytic vaginosis" remains a controversial entity and there is lack of evidence to attribute the symptoms to overgrowth of lactobacilli.[17] The authors also stressed the need for a more accurate diagnostic criteria.[17]

CLINICAL FEATURES AND DIAGNOSIS

The common symptoms associated with cytolytic vaginosis include whitish vaginal discharge, vulvar erythema, pruritus, dyspareunia, and vulvar dysuria.[3] The symptoms are more during the luteal phase of the menstrual cycle.[3] Cibley and Cibley proposed the diagnostic criteria for cytolytic vaginosis in 1991 [Table 2].[3]

Cytolytic vaginosis should be distinguished from other conditions that manifest with vaginal discharge, vulvovaginal pruritus, burning, irritation, or odor [Table 3].[3,7,18]

Most of the authors have found it almost impossible to clinically differentiate between cytolytic vaginosis and vulvovaginal candidiasis. Hu *et al*., after studying 21 healthy women, 33 patients with cytolytic vaginosis and 54 patients with vulvovaginal candidiasis concluded that assessment of vaginal smears with respect to the quantity of lactobacilli, epithelial cell morphology, and absence or presence of *Candida*, *Trichomonas vaginalis* and clue cells is the way to differentiate cytolytic vaginosis from other conditions that can present with similar symptoms.[19]

However, Yang *et al*., after studying 143 patients with cytolytic vaginosis and 196 patients with recurrent vulvovaginal candidiasis reported certain clinical features that could distinguish between the two.[8] The authors found that the vaginal mucosa showed more inflammation in patients with candidiasis, while slight swelling or erythema of the vulva was more common in those with cytolytic vaginosis. Authors attributed the vulvar signs in cytolytic vaginosis to the etching with excess levels of lactic acid. They also observed a greater quantity of vaginal discharge (that filled or overflowed the vagina and present at the introitus) in those with cytolytic vaginosis. Contrary to the observation of previous authors (who reported a thick and white discharge in cytolytic vaginosis), Yang *et al*., noted a homogeneous, white, thin, and paste-like discharge in patients with cytolytic vaginosis. A thicker discharge was noted in vulvovaginal candidiasis. Majority of patients with cytolytic vaginosis in their study had a vaginal pH between 3.5 and 4.1, while the majority of those with recurrent vulvovaginal candidiasis had a vaginal pH between 4.1 and 4.4. The authors proposed vaginal pH and quantity of discharge as the two features that could be useful in differentiating cytolytic vaginosis from vulvovaginal candidiasis.[8] The utility of the described features needs evaluation in further studies.

Table 2: Diagnostic criteria for cytolytic vaginosis.

A high index of suspicion
Wet smear showing
(i) Absence of *Trichomonas, Gardnerella*, and *Candida*
(ii) An increased number of lactobacilli (often adherent to the vaginal intermediate epithelial cell)
(iii) A paucity of white blood cells
(iv) Evidence of cytolysis with bare or naked intermediate epithelial cell nuclei
Discharge (which may be white, frothy, or cheesy)
and a pH between 3.5 and 4.5

In cytolytic vaginosis, the lactobacilli in the vaginal smear, often appear adherent to the intermediate epithelial cell, mimicking the clue cells of bacterial vaginosis, and hence are called as false clue cells. The distinction can be made based on the size of the cells. Clue cells (cells of G. vaginalis) are small, pleomorphic rods of size 0.4 μm ×1.0–1.5 μm.[20] False clue cells of lactobacilli are of a length of approximately 1–1.5 μm and a diameter of approximately 0.7–1 μm.[21]

Spiegel *et al*., proposed a scoring system for lactobacilli (large gram-positive bacilli) in gram-stained smears as follows.[22]

1+ <1 bacilli/oil immersion field
2+ 1–5/oil immersion field
3+ 6–30/oil immersion field
4+ >30/oil immersion field.

TREATMENT

Treatment of cytolytic vaginosis aims to increase the vaginal pH. Cibley and Cibley recommended sodium bicarbonate

Table 3: Conditions manifesting vaginal discharge, vulvovaginal pruritus, burning, irritation, or odor.

Parameter considered		Characteristic finding in individual condition
pH of vaginal secretions		3.5–4.5 in cytolytic vaginosis, >4.5 in bacterial vaginosis, <5 in vulvovaginal candidiasis, >4.5 or at times normal pH in trichomoniasis
A drop of 10% potassium hydroxide (KOH) added to vaginal discharge (on a glass side)		Fishy odor (Whiff test positive) in bacterial vaginosis
Microscopy of vaginal smear	Wet mount	**Trichomoniasis** Motile trichomonads, abundant white blood cells **Bacterial vaginosis** "Clue cells" (epithelial cells with borders obscured by small, anaerobic bacilli), a few white blood cells **Cytolytic vaginosis** "False clue cells" (the lactobacilli adherent to intermediate epithelial cells), a few white blood cells, cytoplasmic fragmentation due to lysis of cells, bare or naked intermediate epithelial cell nuclei **Vulvovaginal candidiasis** Hyphae/psuedohyphae/spores
	10% KOH smear	**Vulvovaginal candidiasis** Hyphae/pseudohyphae/spores
	Gram stain	**Bacterial vaginosis** Abundant gram-negative coccobacilli, a few white blood cells, a few or absent lactobacilli (gram positive) **Cytolytic vaginosis** Abundant lactobacilli, absent coccobacilli, a few white blood cells **Vulvovaginal candidiasis** Few or absent coccobacilli, lactobacilli within normal limits, abundant white blood cells.

Abundant white blood cells in the vaginal smear in bacterial vaginosis indicate coexisting gonococcal/chlamydial infections, trichomoniasis, or vulvovaginal candidiasis

douches (30–60 g sodium bicarbonate in 1 liter of warm water) 2–3 times/week, which was then tapered to a frequency of once or twice a week. Suppository of gelatin capsules filled with baking soda is also reported to be effective.[7] The capsules are inserted intravaginally twice a week, every 2 weeks. A re-evaluation is recommended in case of persistence or worsening of symptoms beyond 2–3 weeks of initiation of treatment.[11]

CONCLUSION

Cytolytic vaginosis remains a less discussed and less studied entity. Some consider that many of the patients diagnosed as treatment-resistant, vulvovaginal candidiasis could actually be suffering from cytolytic vaginosis. There is a need to improve awareness regarding this entity among clinicians to offer relief to the affected. A microscopy of vaginal smear may help to differentiate cytolytic vaginosis from vulvovaginal candidiasis. But others have questioned its existence as a distinct entity and called for more reliable diagnostic criteria. In this review, we have tried to draw attention to the entity of cytolytic vaginosis, so that more information can be attained regarding the condition in different population groups.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest

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